

Remarks

Claims 1-65 were pending. By this amendment, claims 4, 11, 12, 34 and 42-65 are cancelled without prejudice to prosecution in a future application. No claims are added. Therefore, claims 1-3, 5-10, 13-33, 35-41 and 66-67 are now pending.

Support for the claim amendments and new claims can be found throughout the specification, for example:

Claim 1: original claims 4, 11 and 12.

Claim 66: page 5, line 29 – page 6, line 23; page 17, lines 8-10.

Claim 67: page 32, lines 29-32.

No new matter is introduced by these amendments, and no amendments were made to distinguish prior art.

Objections to the Specification

The specification was objected to on the ground that the ATCC deposition numbers were missing. The specification is amended to include this information (PTA-6411).

The specification was also objected to on the ground that the specification recites GenBank accession numbers, but that such sequences can change over time. It was requested that SEQ ID NOS: be sued to identify these sequences. Applicants disagree and request reconsideration. The reference to GenBank accession numbers in the present application is merely to demonstrate that such sequences were well-known in the art, and were publicly available as of the priority date of this application. It is of no consequence that these sequences change over time. As these sequences are in the public domain, Applicants are not required to include them in the specification by sequence identifiers.

The specification was also objected to due to a typographical error in paragraph [0169]. This paragraph has been amended to recite SEQ ID NO: 28 instead of SEQ ID NO: 24.

In view of these explanations and amendments, Applicants request that the objections to the specification be withdrawn.

Objections to the Claims

Claims 3 and 13-15 were objected to on the ground that they recited non-elected SEQ ID NOS: 17, 21 and 23. These sequence identifiers have been deleted.

In view of these amendments, Applicants request that the objections to claims 3 and 13-15 be withdrawn.

35 U.S.C. § 112, first paragraph: written description

Claims 1-41 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants disagree and request reconsideration.

Claim 1 has been amended to specify that the claimed cells that are capable of producing beta-alanine from alpha-alanine have both an exogenous nucleic acid molecule encoding a beta-alanine/pyruvate aminotransferase having at least 90% sequence identity to SEQ ID NO: 20 and an exogenous nucleic acid molecule encoding an alanine 2,3-aminomutase. As described below, the specification provides written description for numerous different cell types, as well as particular examples of beta-alanine/pyruvate aminotransferase enzymes and alanine 2,3-aminomutase enzymes.

It is asserted that the claims are directed to a genus of cells from any source, the include enzyme activities selected from a beta-alanine/pyruvate aminotransferase, 3-hydroxypropionate dehydrogenase, alanine 2,3-aminomutase, lipase, esterase, aldehyde dehydrogenase and alcohol dehydrogenase, wherein the cells produce 3-hydroxypropionic acid (3-HP) from beta-alanine. It is further asserted that the specification does not teach the structure of a representative number of cells types or polynucleotides encoding proteins with the particular enzyme activities.

Applicants disagree for at least the following reasons.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. In addition, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would

not recognize in the disclosure a description of the invention defined by the claims"). Here, the specification sufficiently describes cells and enzymes that are needed for the cells to produce 3-hydroxypropionic acid (3-HP) from beta-alanine. Thus, Applicants have satisfied the written description requirement.

First, the specification specifically provides numerous specific examples of cells that can be used to express enzymes with the desired activity to produce 3-HP. For example, page 19, lines 1-11 and page 25, lines 1-18 provide specific examples of cells that are encompassed by the claims. For example, the cells that produce 3-HP can be mammalian cells (such as human, murine, and bovine cells), plant cells (such as corn, wheat, rice, and soybean cells), fungal cells (such as *Aspergillus* and *Rhizopus* cells), yeast cells, algae cells, fungal cells, protozoa, or bacterial cells (such as *Lactobacillus*, *Lactococcus*, *Bacillus*, *Escherichia*, and *Clostridium* cells). Although the specification only provides actual reduction to practice for *E. coli*, one skilled in the art would expect that the other cell types specifically mentioned in the specification, in addition to *E. coli*, could be used. Therefore, there is adequate written description for numerous different types of cells.

Second, the specification specifically provides numerous specific examples of enzymes that can be used to produce 3-HP in a cell. For example, specific enzyme sequences that can be used in the claimed cells are provided in the section entitled "Enzymes" that begins on page 21. Additional specific examples of beta-alanine/pyruvate aminotransferase sequences that can be used are provided on page 6, line 31 – page 7, line 11; 3-hydroxypropionate dehydrogenase sequences on page 11, lines 14-21; and alanine 2,3-aminomutase sequences on, page 5, line 32 – page 6, line 12. Furthermore, one skilled in the art will recognize based on the written description of the enzymes provided in the application that additional examples of particular enzyme sequences that can be used in the claimed cells can be identified by searching publicly available databases (such as the NCBI website) for these enzymes. Therefore, there is adequate written description for the enzymes listed in the claims.

Given the overall teaching of the specification, that is using a beta-alanine/pyruvate aminotransferase to produce 3-hydroxypropionic acid (3-HP) from beta-alanine, in addition to the specific cells and sequences provided in the application, one skilled in the art has adequate written description for cells having such activity. It is well within the ability of one skilled in the art to select particular cells and enzyme sequences (depending on the needs or goals) to construct

cells within the scope of the invention. For example, methods of expressing nucleic acid sequences in both prokaryotic and eukaryotic cells are very well known to those skilled in the molecular biology arts. With the provision of particular sequences that were successful in *E. coli.*, one skilled in the art can easily transfer these sequences into other cells (*e.g.*, other bacterial cells or yeast cells). In addition, it is routine in the art to optimize codons in a given sequence depending on the organism in which the sequence is to be expressed, in addition, other parameters in a sequence can be modified to optimize expression in a particular cell type. Again, these methods are routine in the art.

It is also asserted that the specification does not provide examples of enzyme sequences having variant sequences that retain enzyme activity. Applicants disagree. The specification provides several examples of each enzyme, and those examples have varying degrees of sequence identity, as shown below:

beta-alanine/pyruvate aminotransferase protein sequences: SEQ ID NO: 18 and 20 have 76.6% sequence identity (see Exhibit A);

3-hydroxypropionate dehydrogenase sequences: SEQ ID NO: 28 (GenBank Accession No: AAG06957) and GenBank Accession No: AAA25891 have 14% sequence identity (see Exhibit B);

alanine 2,3-aminomutase sequences SEQ ID NOS: 22 and 24 and 26 have 59 % to 100 % sequence identity (see Exhibit C).

In addition, one skilled in the art based on the teachings of the application and the knowledge in the art would be able to generate a sequence having at least 90% sequence identity to a given sequence, and test whether that sequence has the desired enzyme activity.

It is asserted on page 5 of the Office action that specification indicates that it is advantageous to delete the lactate dehydrogenase gene in the claimed cells. Applicants agree that it can be advantageous to functionally delete the lactate dehydrogenase in the claimed cells, as it (as well as other enzymes) competes with the beta-alanine/pyruvate aminotransferase for pyruvate, thus decreasing detectable 3-HP production. However, it is not Applicants' position (nor stated as such in the specification) that the lactate dehydrogenase must be deleted in order to

produce the desired product. Instead, it is merely an exemplary embodiment that permits enhanced production of 3-HP or other downstream product.

35 U.S.C. § 112, first paragraph: enablement

Claims 1-41 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants disagree and request reconsideration.

It is asserted that because the only examples actually reduced to practice include *E. coli* cells that lack the lactate dehydrogenase gene and express (1) beta-alanine/pyruvate aminotransferase (SEQ ID NO: 19) and 3-hydroxypropionate dehydrogenase (SEQ ID NO: 27) or (2) beta-alanine/pyruvate aminotransferase (SEQ ID NO: 19) and 3-hydroxypropionate dehydrogenase (SEQ ID NO: 27) and alanine 2,3-aminomutase (SEQ ID NO: 21) does not provide enablement for any other cell type other than the specific strain used to produce 3-HP. Applicants disagree.

The broadest claims are directed to cells that express an exogenous nucleic acid molecule encoding a beta-alanine/pyruvate aminotransferase having at least 90% sequence identity to SEQ ID NO: 20, and an exogenous nucleic acid encoding an alanine 2,3-aminomutase, wherein the cells can produce 3-HP from beta alanine. Example 4 shows that expression of beta-alanine/pyruvate aminotransferases from either *P. aeruginosa* or *P. putida* (SEQ ID NOS: 19 and 17, respectively) (even in the absence of an exogenous 3-hydroxypropionate dehydrogenase or alanine 2,3-aminomutase) in *E. coli* permits production of 3-HP (see page 36, lines 16-23). Therefore, the results show that expression of two different beta-alanine/pyruvate aminotransferases having only 76.6% sequence identity can be used to produce 3-HP in the cells of a non-native organism. Based on these results, one skilled in the art would expect that variant sequences can be used (*e.g.*, those having at least 90% sequence identity to those disclosed), and that other cell types could be used. For example, one skilled in the art would expect similar results in at least the organism from which the particular beta-alanine/pyruvate aminotransferase was obtained (*i.e.*, *P. aeruginosa* or *P. putida*).

It is asserted on page 9 of the Office action that specification only discloses examples where the lactate dehydrogenase gene is deleted. As discussed above, it is not Applicants' position that the lactate dehydrogenase must be deleted in order to produce the desired product. Instead, it is merely an exemplary embodiment that permits enhanced production of 3-HP or

other downstream product. One skilled in the art would expect less 3-HP production in the presence of lactate dehydrogenase as it competes with the exogenous beta-alanine/pyruvate aminotransferase for pyruvate. However, the cells will still produce 3-HP in the presence of lactate dehydrogenase.

The specification is sufficiently enabled for cells of any type to produce 3-HP using the enzyme sequences provided in the application, as well as those sequences known in the art at the time of the invention, or identified after the invention. As discussed above, the specification provides several examples of particular sequences for each enzyme. In addition, other examples were available as of the priority date of the application. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Furthermore, as methods of manipulating sequences to generate variant sequences, methods of transfecting cells, and methods of growing cells are well known to those of skill in the molecular biology arts, the specification provides sufficient enablement for the cells that express 3-HP from beta alanine.

35 U.S.C. § 102(e)

Claims 1, 5-7 and 11-41 were rejected under 35 U.S.C. § 102(e) as anticipated by claims 18, 19, 26-35 of US Patent No. 7,309,597.

Although Applicants disagree, solely in order to expedite prosecution the claims now recite particular beta-alanine/pyruvate aminotransferase sequences not found in the cited patent (*e.g.*, claim 1 now recites that the exogenous nucleic acid molecule encoding a beta-alanine/pyruvate aminotransferase has at least 90% sequence identity to SEQ ID NO: 20). In view of the amendments, Applicants request that the 35 U.S.C. § 102(e) rejection be withdrawn.

Double Patenting

Claims 1, 5-7 and 11-41 were rejected on the ground of non-statutory obviousness-type double patenting as unpatentable over claims 18, 19, and 26-35 of US Patent No. 7,309,597.

Although Applicants disagree, solely in order to expedite prosecution the claims now recite particular beta-alanine/pyruvate aminotransferase not found in the cited patent (*e.g.*, claim 1 now recites that the exogenous nucleic acid molecule encoding a beta-alanine/pyruvate aminotransferase has at least 90% sequence identity to SEQ ID NO: 20). In view of this amendment, Applicants request that the double patenting rejection be withdrawn.

Examination of Additional Species

As generic claim 1 is now in condition for allowance, Applicants request consideration of claims to the non-elected species (including SEQ ID NOS: 17, 21 and 23) as per 37 C.F.R. § 1.141.

As the claims are in condition for allowance, a Notice of Allowance is requested. If there are any questions regarding this response, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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